APCN x TSN 2025
23rd Asian Pacific Congress of Nephrology
Gene, Immunology, Vast, MEtabolism at its Finest!
2025 Dec. 5 Fri. ▶ 7 Sun.
TaiNEX 2, Taipei, Taiwan

APSN ISN Joint Symposium：“The Intersection of Global Health, Metabolism, and Kidney Disease”

# Advancing the Biology of Diabetic Kidney Disease: Mechanisms and Therapeutic Perspectives

Masaomi Nangaku
Immediate Past President of the ISN
Past President of the APSN
President of the JSN
Dean, The University of Tokyo Graduate School of Medicine

# COI disclosure: financial presenter: Masaomi Nangaku

I have the following relationships to disclose.

- Employment: No
- Stock ownership or options: No
- Patent royalties/licensing fees: No
- Honoraria and advisory fees: Kyowa-Kirin, Mitsubishi-Tanabe, Bayer
- Research funding: Kyowa-Kirin, BI, JT, Chugai, Mitsubishi-Tanabe, Torii

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# 2024 Taiwan clinical practice guideline for diabetic kidney disease – an executive summary

Sheng-Chiang Su [a], Tieng-Chun Chang [b], Yi-Wen Chiu [c,d], Chih-Hsun Chu [e], Yueh-Han Hsu [f], Chin-Sung Kuo [g,h], Chun-Chuan Lee [i,j], Ming-Hsun Lin [a], Chun-Liang Lin [k,l,m], Yuh-Feng Lin [n,o], Da-Wei Lin [p], Hui-Yu Peng [q], Shwu-Pyng Su [e], Yi-Chun Tsai [c,r], Yao-Hsien Tseng [s,t], Jun-Sing Wang [s,u], Tsai-Jung Wang [v], Yi-Sun Yang [w], Chien-Ning Huang [w,*], Horng-Yih Ou [x,y,**], Mai-Szu Wu [z,aa,ab,ac,***]

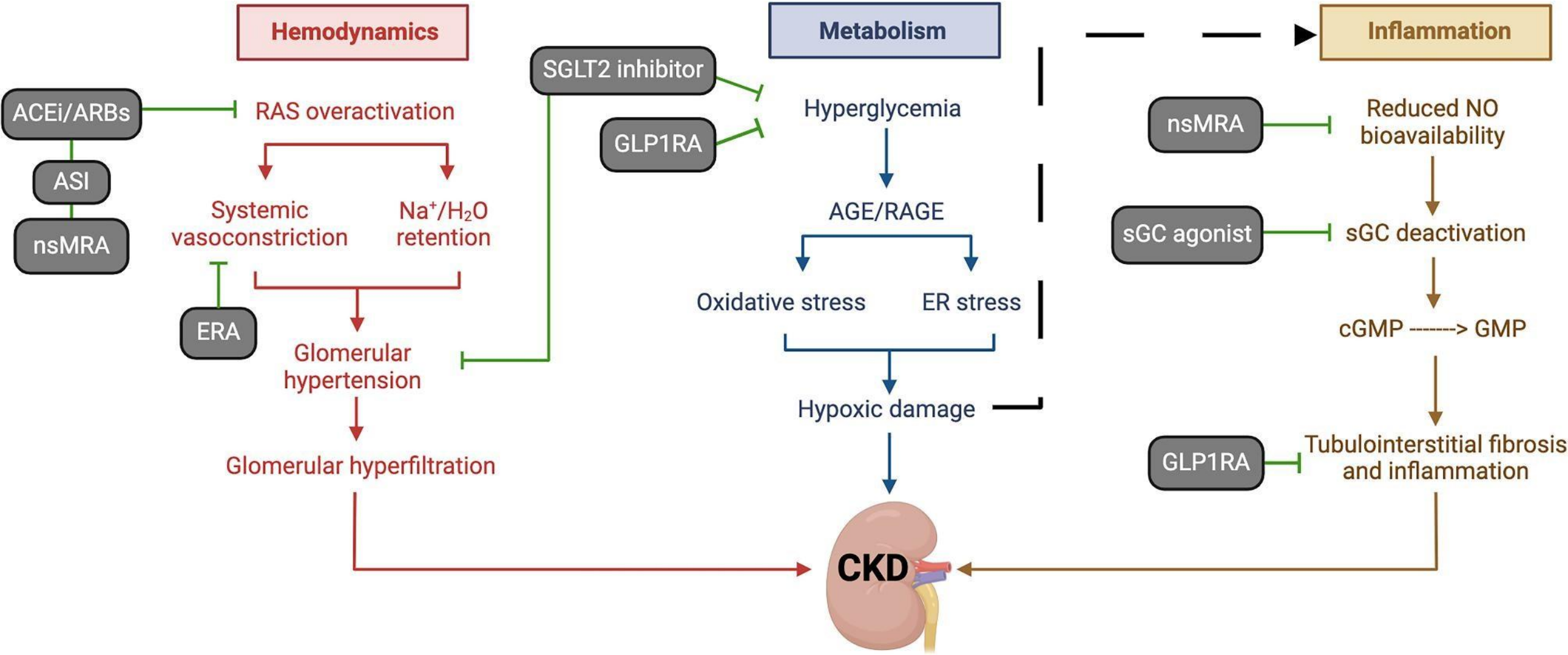
**Su et al. J Formos Med Assoc e-Pub**

Recommendations on use of cardiorenal protective medications in DKD patients.

| Recommendations | Class |
|---|---|
| For DKD patients with eGFR $\geq$20 mL/min/1.73m$^2$, we recommend use of **SGLT2i** to reduce the occurrence of cardiovascular events and renal disease progression. | Strong |
| For DKD patients, **GLP1 RA** is recommended to reduce occurrence of cardiovascular events and renal disease progression. | Strong |
| For DKD patients especially those with albuminuria, use of **nsMRA** in addition to maximum tolerated dose of **ACEi or ARB** can lower cardiovascular risks and slow renal disease progression. | Strong |

**Su et al. J Formos Med Assoc e-Pub**

# Putative mechanisms of action of drugs to mitigate CKD progression




Nardone, Cherney et al. Nephrol Dial Transplant 2025

The NEW ENGLAND JOURNAL of MEDICINE

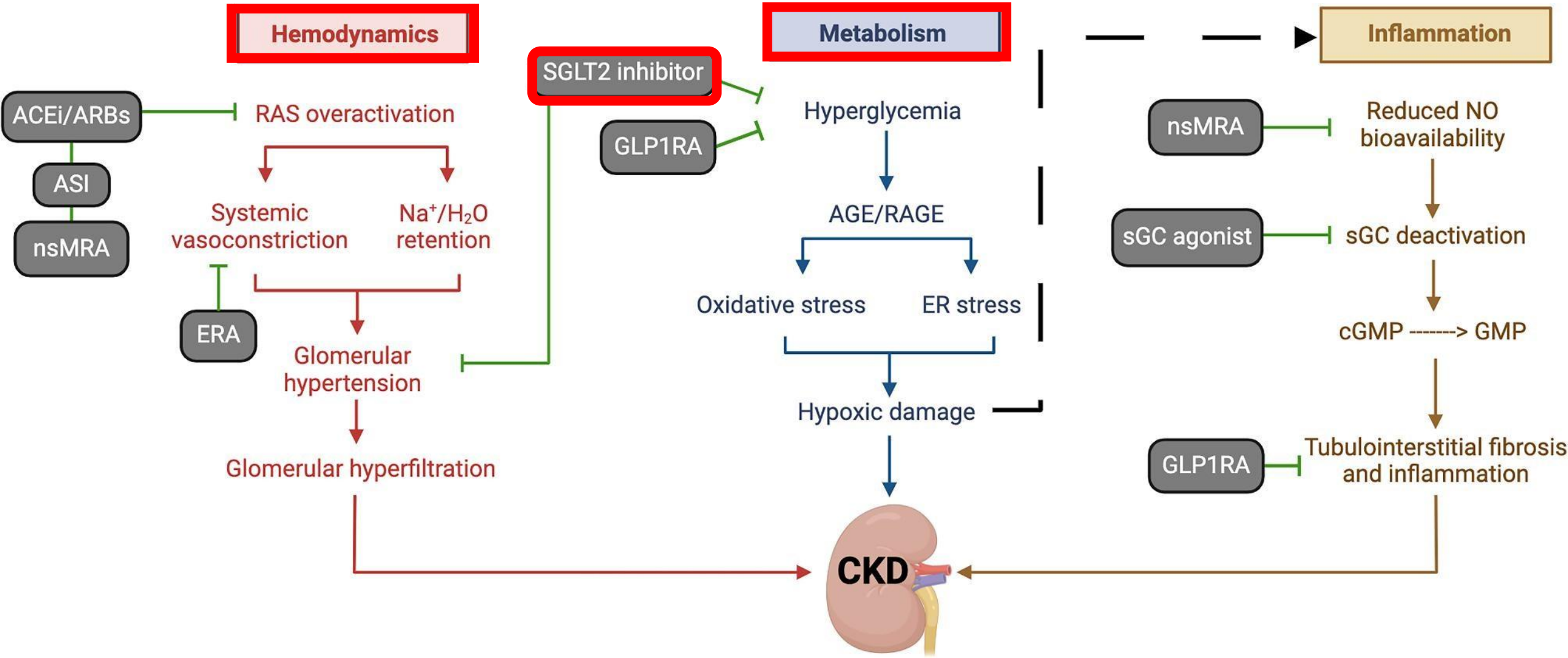
# Empagliflozin in Patients with Chronic Kidney Disease

Herrington, Nangaku et al.
The EMPA-KIDNEY Collaborative Group
N Engl J Med 2023

# Long-Term Effects of Empagliflozin in Patients with Chronic Kidney Disease

Herrington, Nangaku et al.
The EMPA-KIDNEY Collaborative Group
N Engl J Med 2025

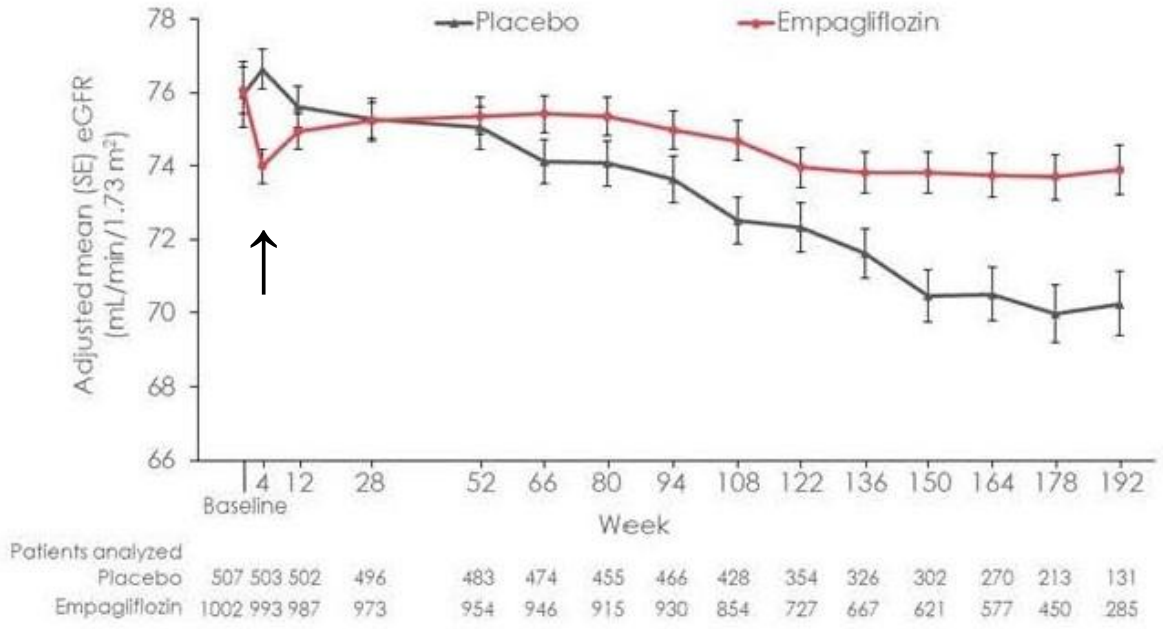
# Putative mechanisms of action of drugs to mitigate CKD progression




Nardone, Cherney et al. Nephrol Dial Transplant 2025

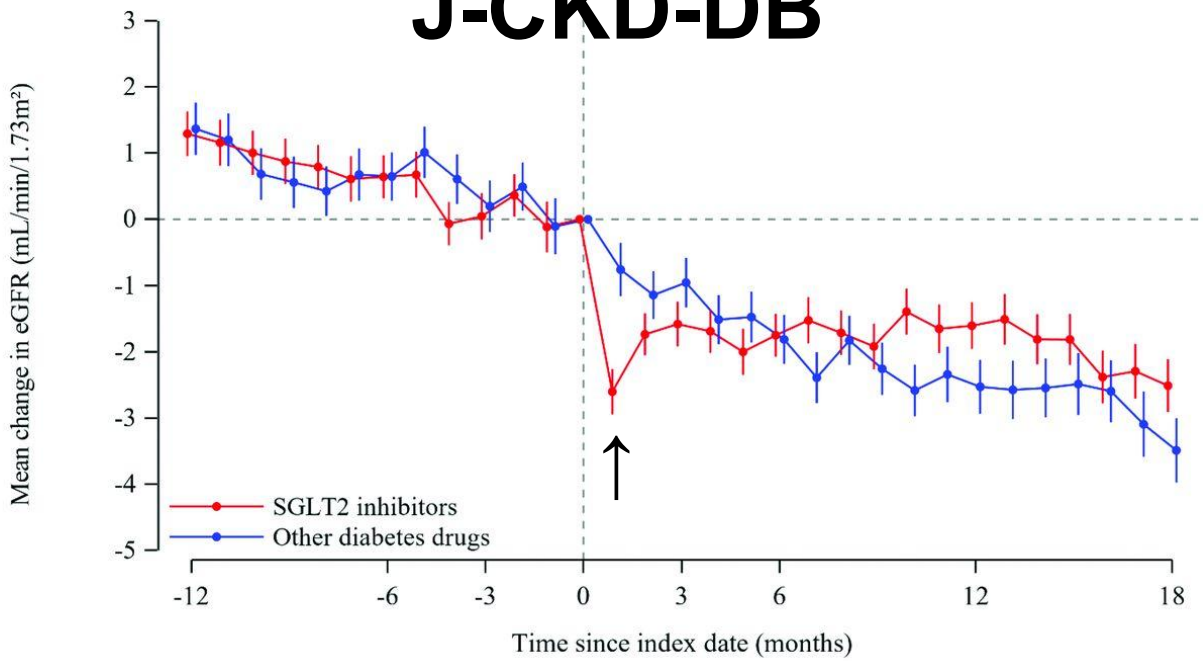
# Initial dip of eGFR by SGLT2 inhibitor

## EMPA-REG OUTCOME




Kadowaki, Nangaku et al.
J Diabetes Invest 2019

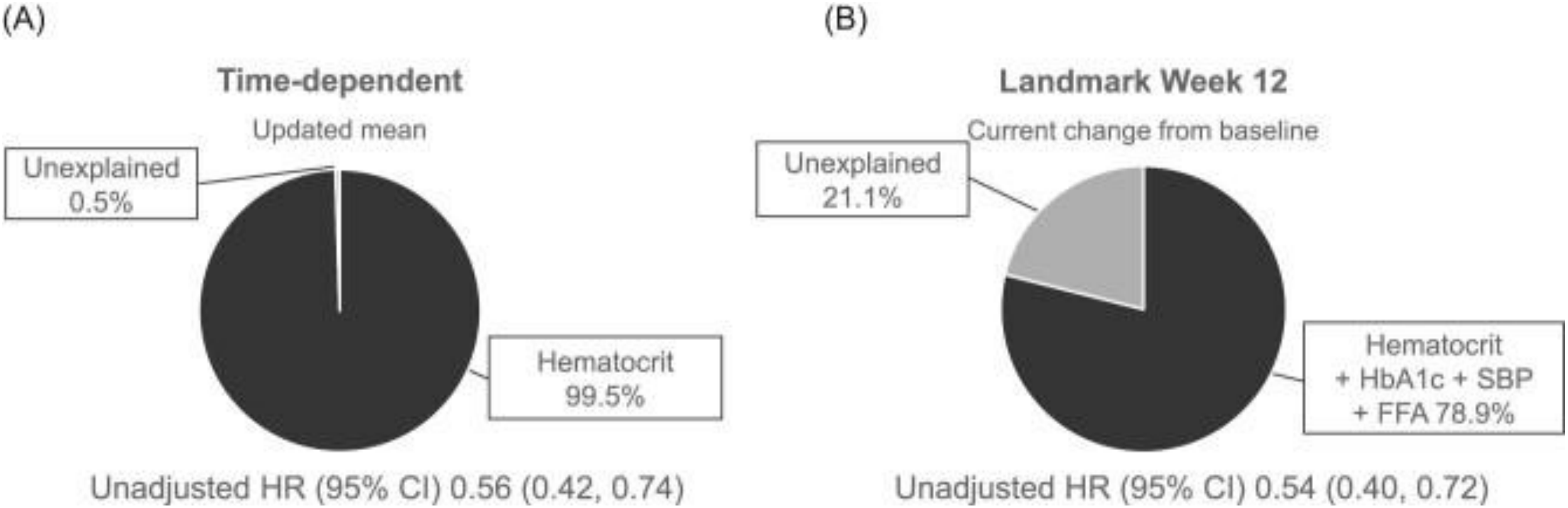
## J-CKD-DB




Nagasu, Nangaku et al.
Diabetes Care 2021

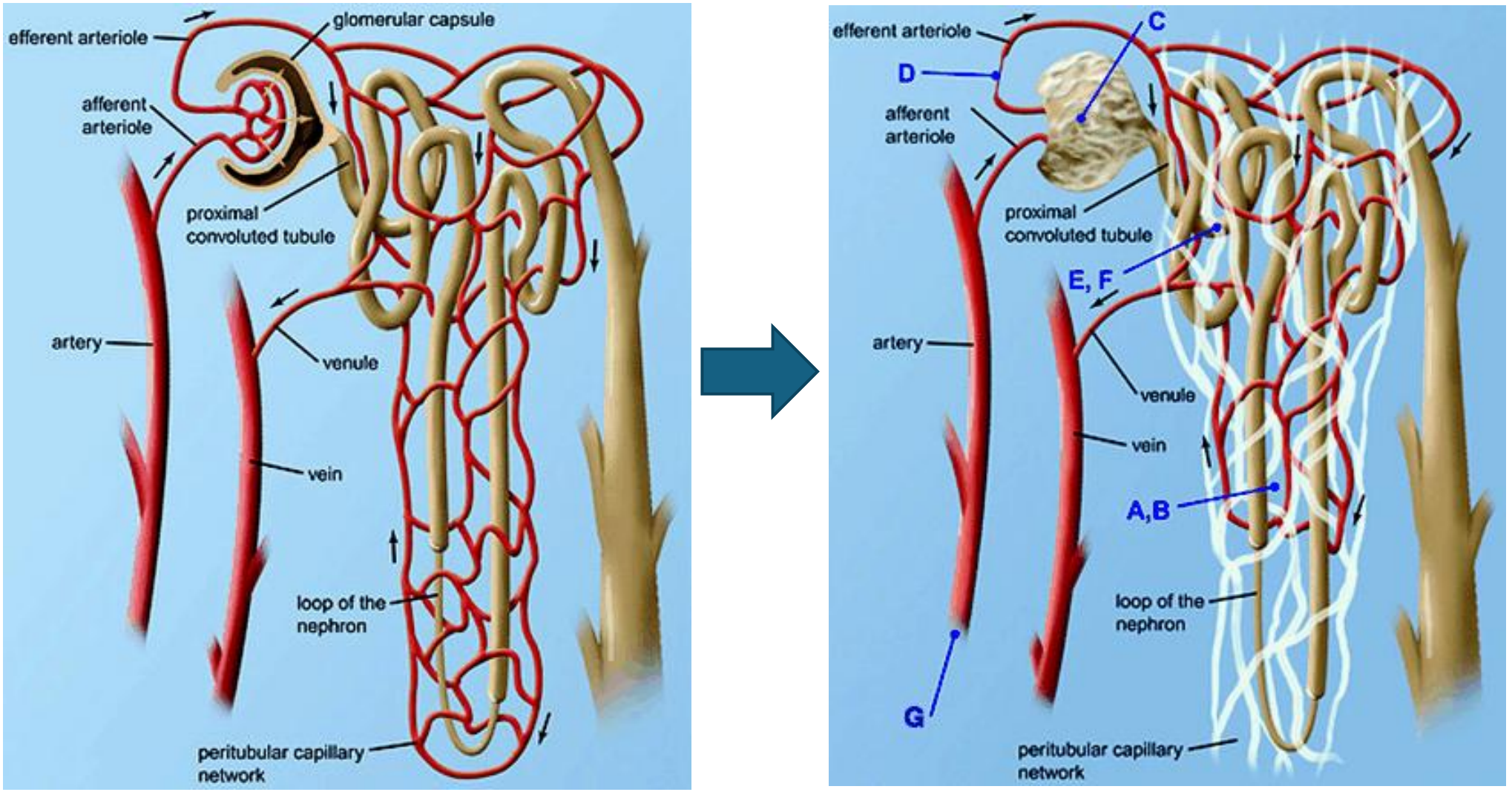
# A mediation analysis of the EMPA-REG OUTCOME trial

## Changes in hematocrit and hemoglobin were the strongest mediators of empagliflozin's kidney benefits in EMPA-REG OUTCOME



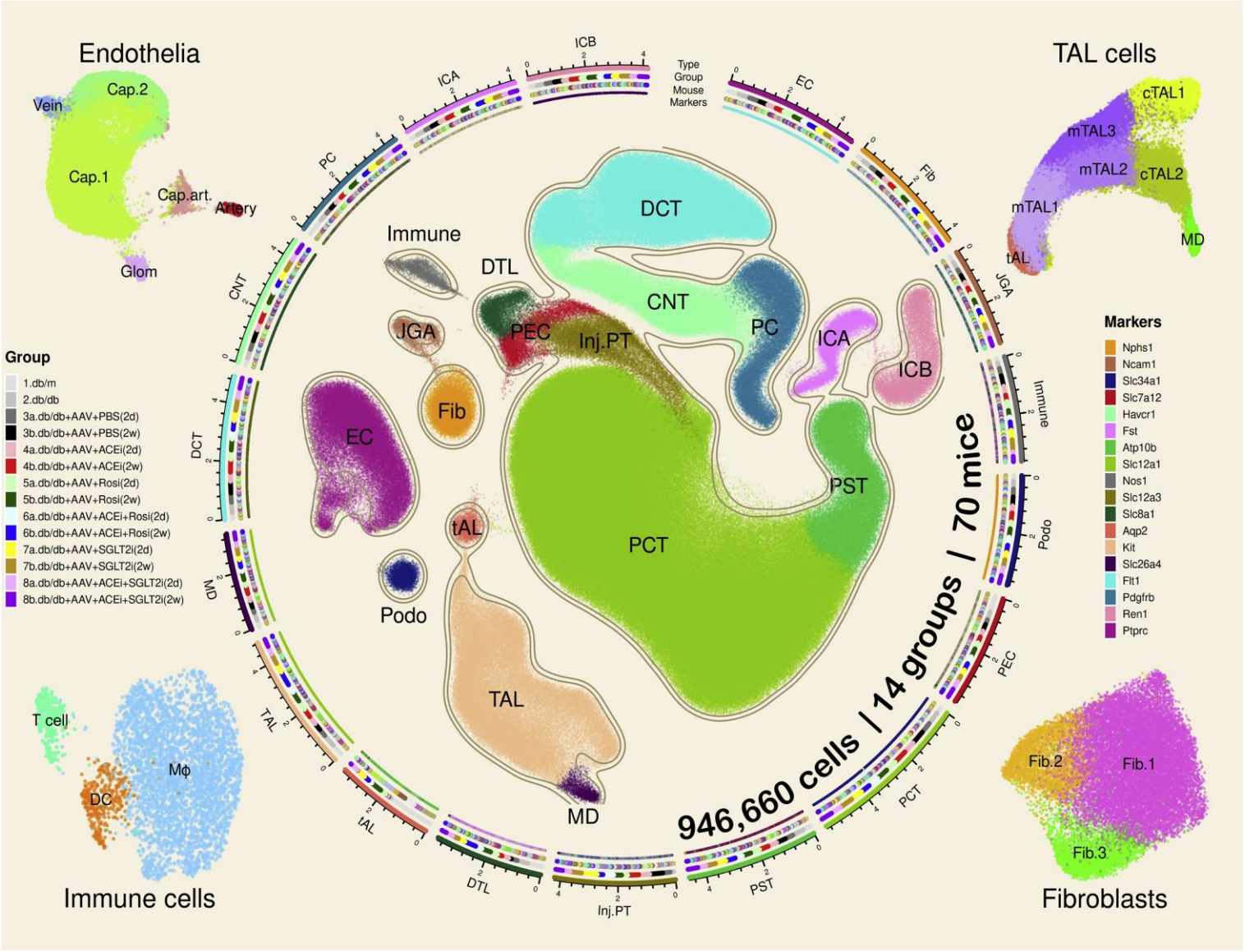

Wanner, Nangaku et al. Nephrol Dial Transplant 2024

# Hypoxia as the final common pathway to End Stage Kidney Disease




Nangaku. J Am Soc Nephrol 2006

# Single-cell atlas of drug treatments in a mouse model of DKD

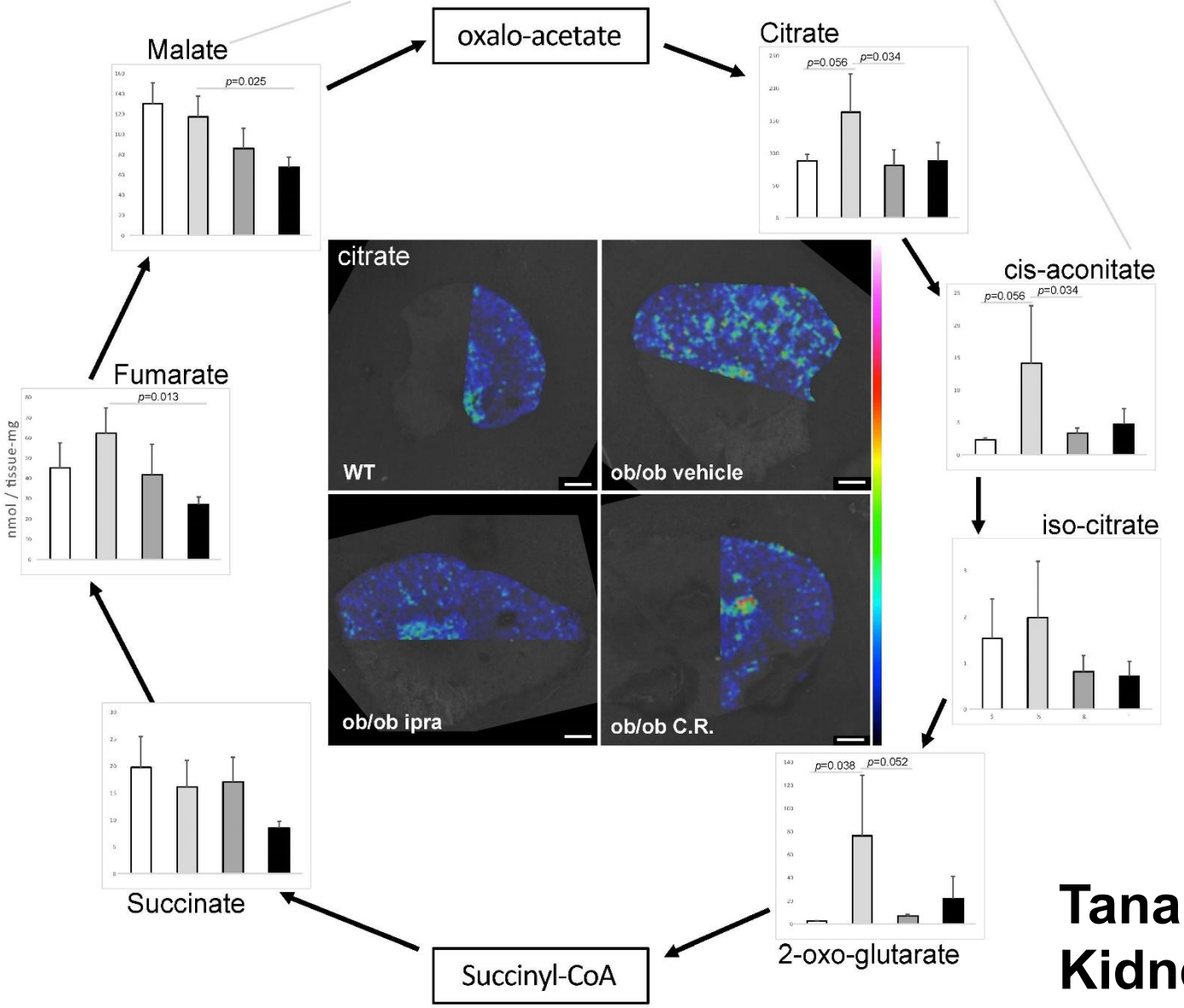



**The early effects of SGLT2i on the S1 segment of the proximal tubule suggest that this drug class induces fasting mimicry and hypoxia responses**

**Wu, Humphreys et al. Cell Metab 2022**

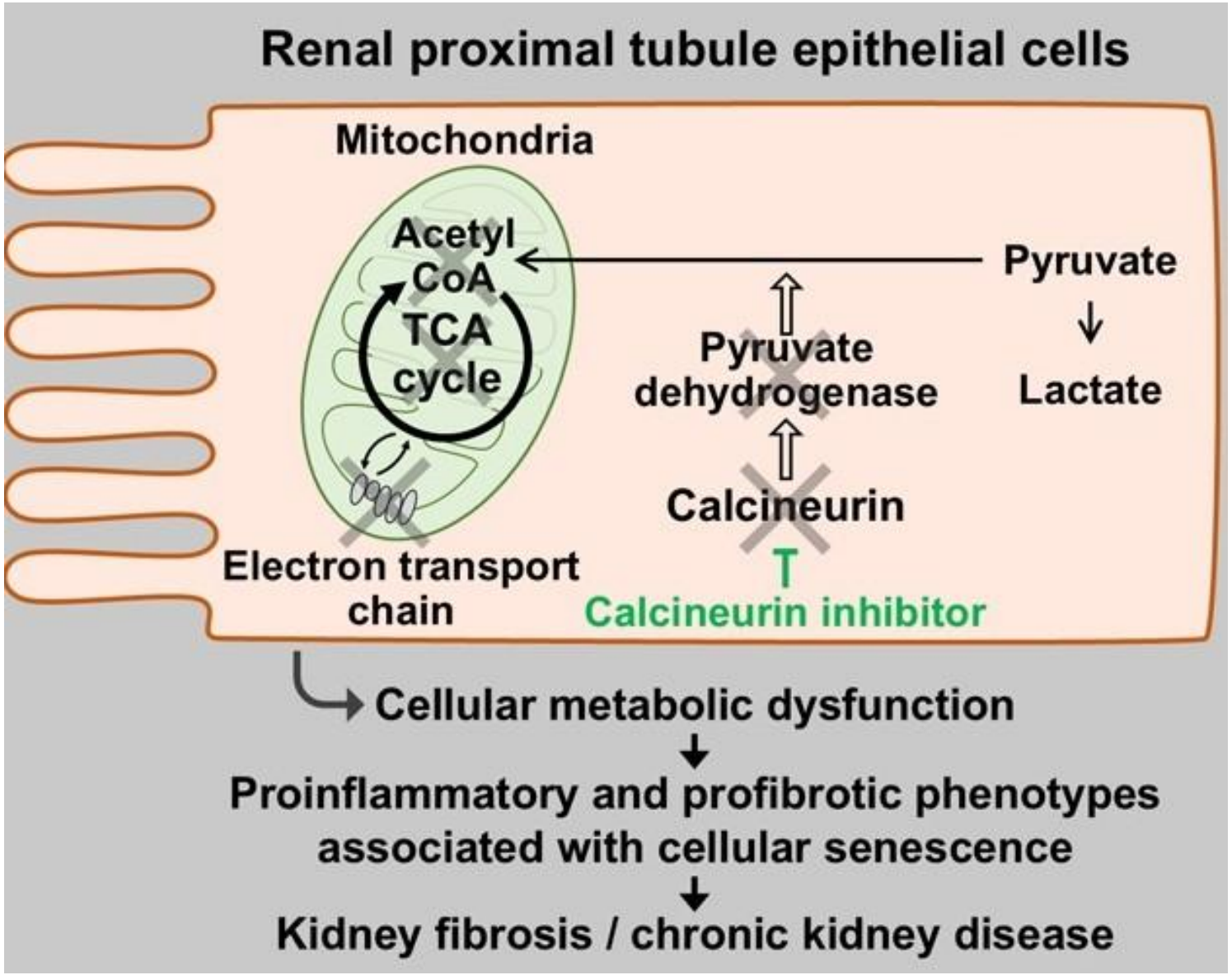
# Accumulation of the TCA cycle metabolites in diabetic kidney

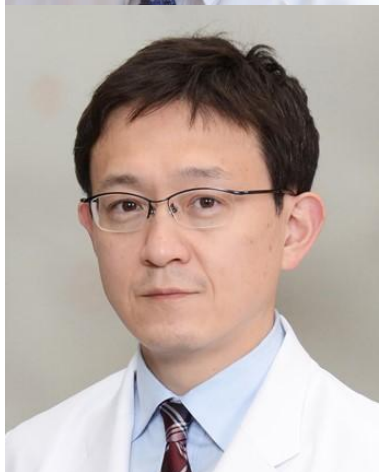
## citrate imaging mass spectrometry data and metabolomics data of the TCA cycle




**Tanaka S, Tanaka T, Nangaku et al. Kidney Int 2018**

# Deactivation of pyruvate dehydrogenase induces proximal tubule cell metabolic dysfunction, causing profibrotic phenotype



Oda, Nishi, Nangaku et al. JASN 2025

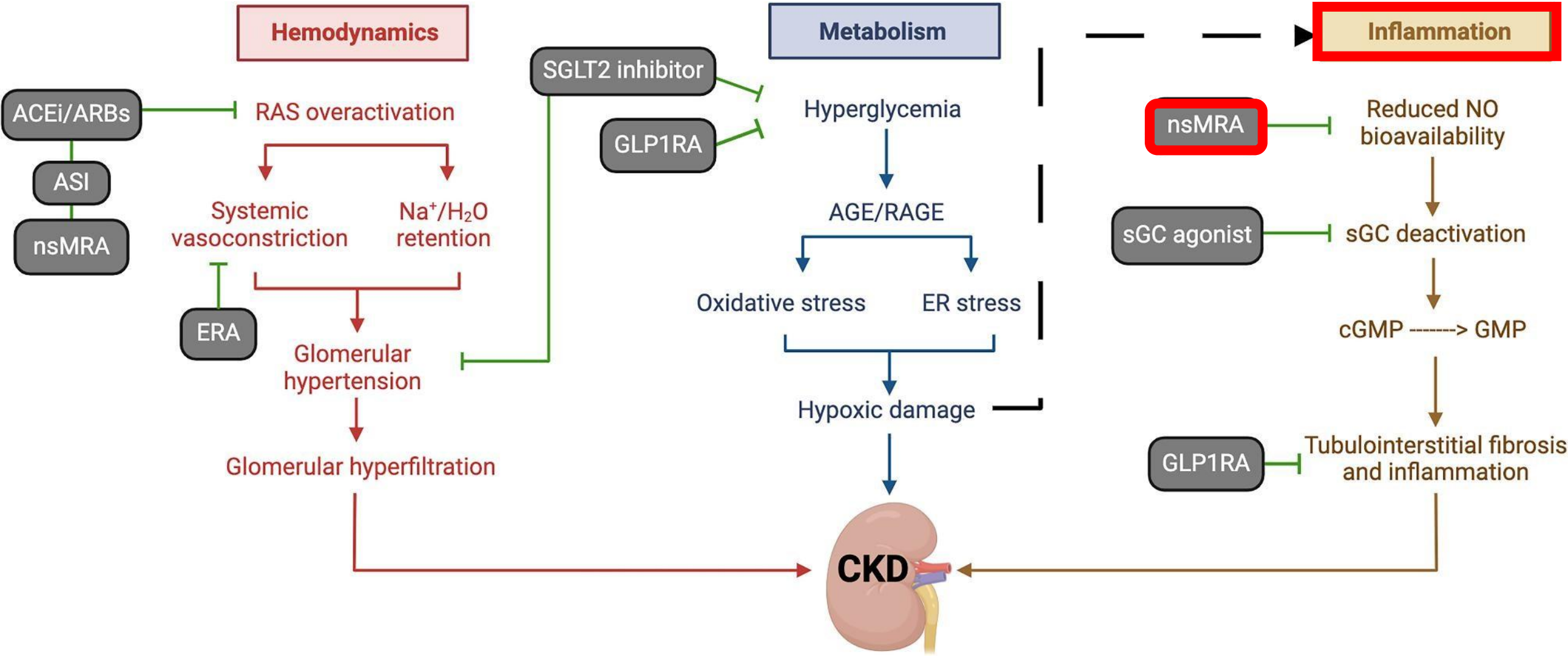
The NEW ENGLAND JOURNAL of MEDICINE

# Finerenone with Empagliflozin in Chronic Kidney Disease and Type 2 Diabetes

**Authors**: Rajiv Agarwal, M.D., Jennifer B. Green, M.D., Hiddo J.L. Heerspink, Ph.D., Johannes F.E. Mann, M.D., Janet B. McGill, M.D., Amy K. Mottl, M.D., Julio Rosenstock, M.D., Peter Rossing, M.D., Muthiah Vaduganathan, M.D., M.P.H., Meike Brinker, M.D., Robert Edfors, M.D., Ph.D., Na Li, M.D., Ph.D., Markus F. Scheerer, Ph.D., Charlie Scott, M.Sc., and Masaomi Nangaku, M.D., Ph.D., for the CONFIDENCE Investigators*

N Engl J Med 2025;393:533-543

# Putative mechanisms of action of drugs to mitigate CKD progression

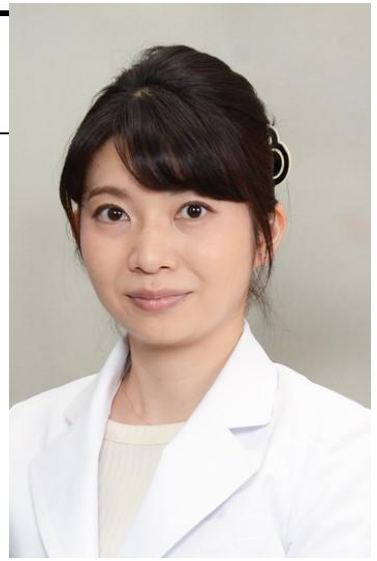



Nardone, Cherney et al. Nephrol Dial Transplant 2025

# Analysis of inflammatory cytokines and eGFR decline in Japanese patients with DKD

## Multivariate analysis demonstrated high levels of LIGHT/TNFSF14, TWEAK/TNFSF12 and sTNF-R2 in rapid decliners

| Predictor | Odds ratio (95% CI) | *P* value |
|---|---|---|
| Age | 1.04 (0.99-1.08) | 0.107 |
| Male | 0.84 (0.38-1.85) | 0.674 |
| eGFR, mL/min/1.73m$^2$ | 1.06 (1.02-1.09) | 0.001 |
| UACR, 10mg/gCre | 1.01 (1.00-1.02) | 0.126 |
| Sample type (Plasma) | 2.63 (0.43-16.16) | 0.296 |
| Chitinase 3-like 1, 4000 pg/mL | 0.78 (0.59-1.05) | 0.098 |
| Chitinase 3-like 1 × sample type interaction | 1.19 (0.90-1.58) | 0.224 |
| LIGHT/TNFSF14, 5 pg/mL | 1.62 (1.14-2.30) | 0.007 |
| LIGHT/TNFSF14 × sample type interaction | 0.91 (0.64-1.28) | 0.579 |
| TWEAK/TNFSF12, 60 pg/mL | 0.65 (0.45-0.92) | 0.016 |
| TWEAK/TNFSF12 × Sample type interaction | 0.74 (0.53-1.05) | 0.095 |
| sTNF-R2, 400 pg/mL | 3.06 (1.20-7.74) | 0.018 |
| sTNF-R2 × sample type interaction | 3.03 (1.21-7.56) | 0.017 |



**Sugawara, Hirakawa, Nangaku et al. Biomark Med 2022**

# *Lysophosphatidylcholine mediates fast decline in kidney function in diabetic kidney disease*

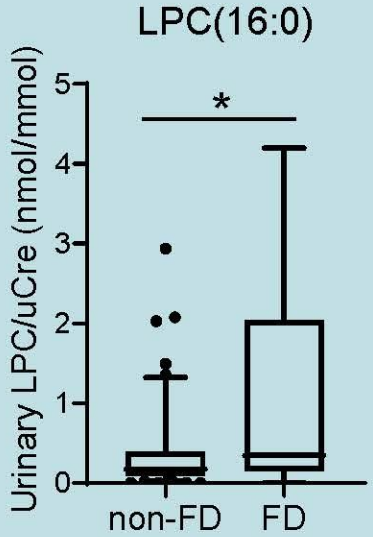
kidney INTERNATIONAL

ISN INTERNATIONAL SOCIETY OF NEPHROLOGY

### *Clinical Cohort*

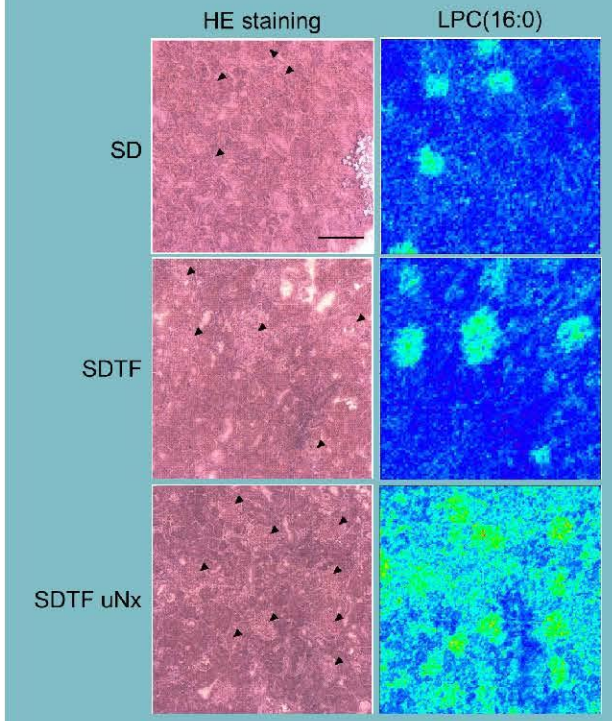
Urinary LPC (16:0) and (18:0) increased in the fast decliner of G3 DKD.

**UT-DKD cohort**



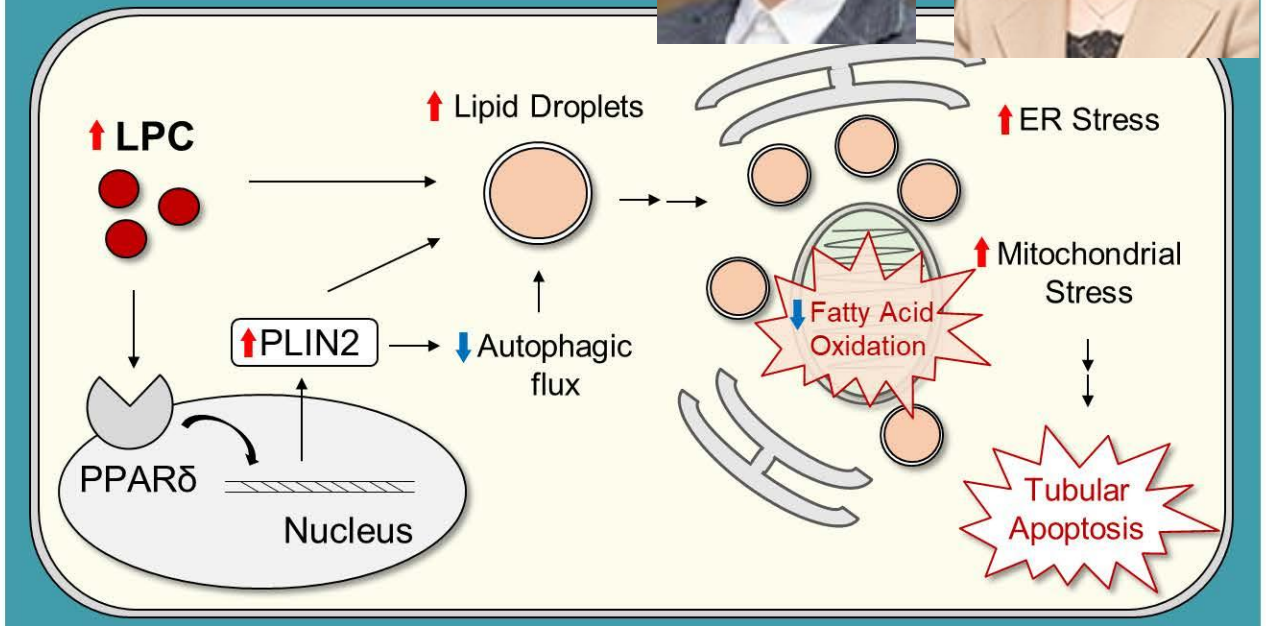

### *Animal models*

LPC accumulates in renal tubulo-interstitium of accelerated DKD rats.




### *Molecular mechanisms*

Tubular accumulation of LPC enhanc re
apoptosis through the PPARδ-PLIN2



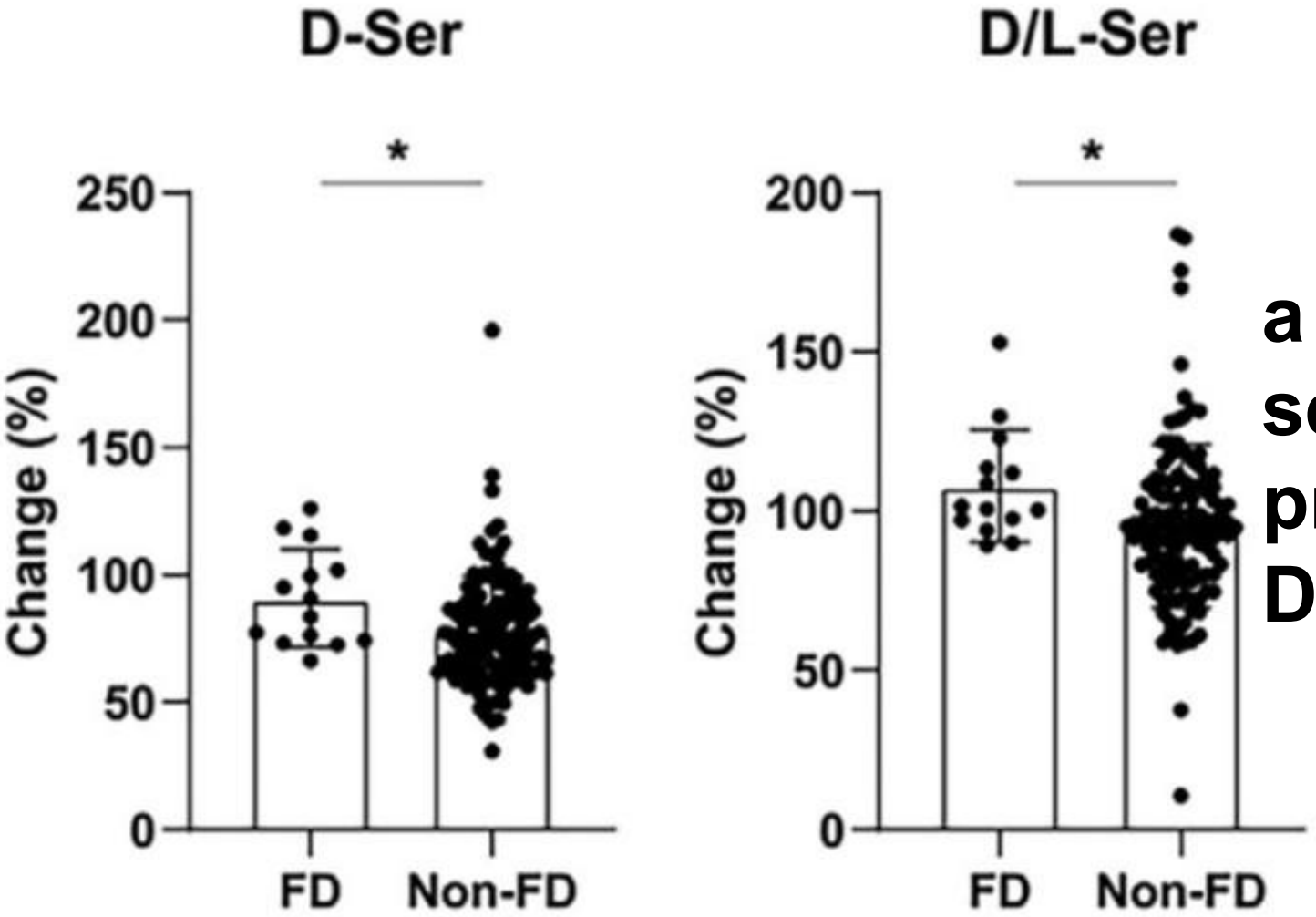

**Yoshioka, Nangaku, Inagi et al. Kidney Int 2021**

## CONCLUSION

LPC (16:0) and (18:0) mediates a fast progression of DKD by accelerating tubular lipotoxicity and may serve as a novel therapeutic target.

# Detection of fast decliner of DKD using chiral amino acid profiling

UT-DKD cohort



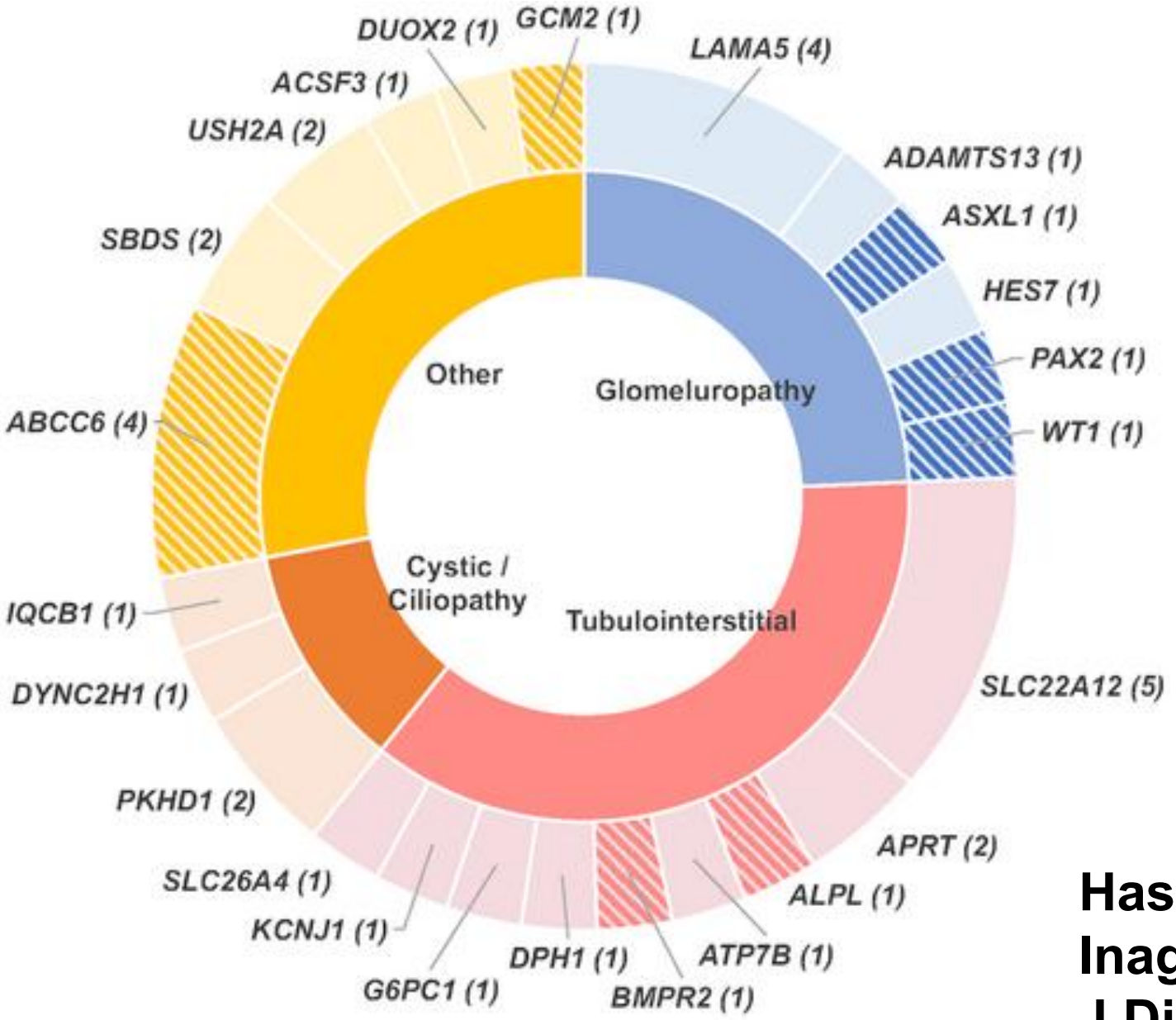




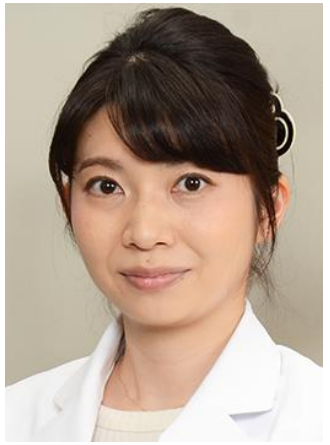
**a short-term increase in D-serine is an independent predictor of early decline in DKD**

Hirakawa, Inagi, Nangaku et al. Chem Biodivers 2025

# Pathogenic variants prevalence patients with DKD in Japan

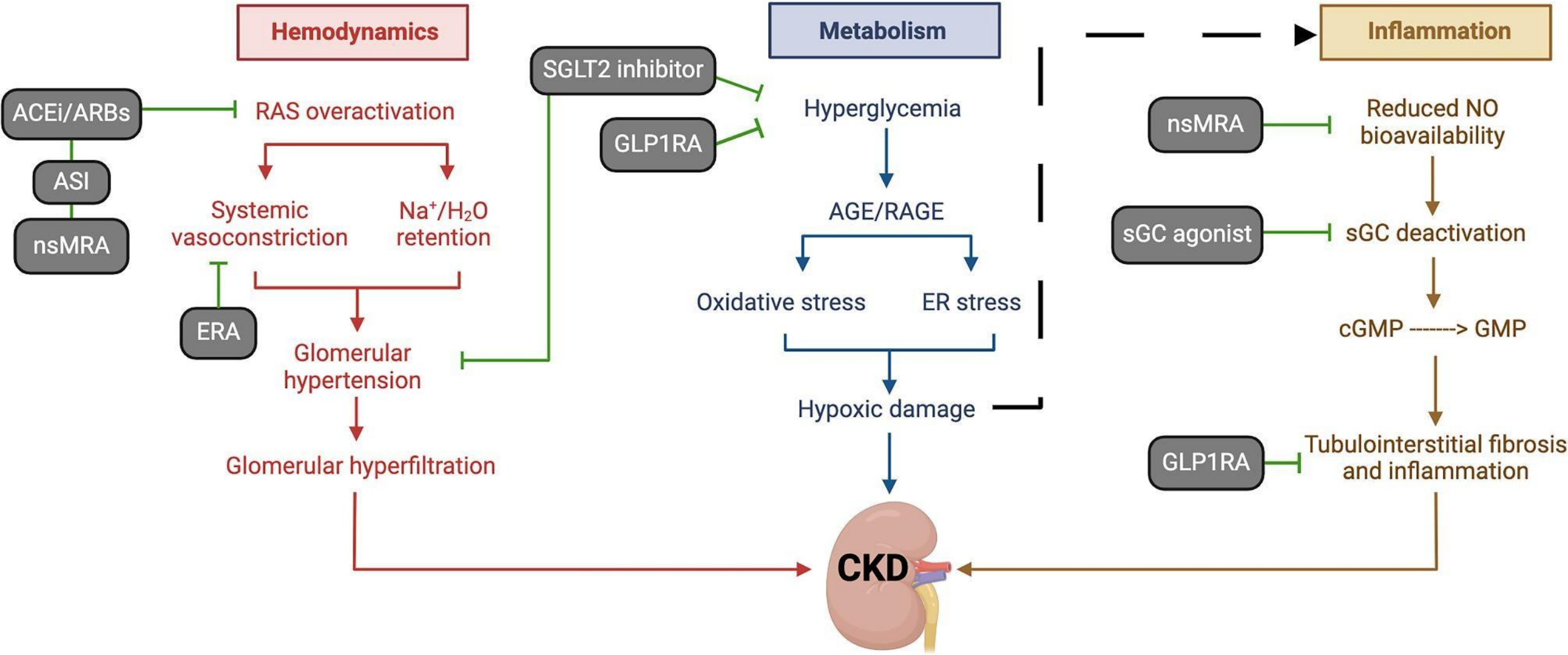



**UT-DKD cohort**



**Hashiba, Sugawara, Hirakawa, Inagi, Nangaku et al.**
**J Diabetes Investig 2025**

# Putative mechanisms of action of drugs to mitigate CKD progression




Nardone, Cherney et al. Nephrol Dial Transplant 2025